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Nine Rheumatoid Factor Assays Compared

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Summary: In this study we have investigated five quantitative and three semi-quantitative rheumatoid factor assays and the *Rose-Waaler* assay in 120 patients suffering from rheumatoid arthritis and in 76 with other systemic diseases. All tests measure the IgM anti-IgG antibodies.

The correlations between the quantitative tests were all higher than 0.86 and much better than between the quantitative and semi-quantitative tests and the semi-quantitative tests themselves (r between 0.22 and 0.85). The within run and between run precision studies for the quantitative tests showed CV values lower than 16%.

In spite of the standardisation on the WHO and the Center of Disease Control Reference Preparation we found important differences in patient results.

From an analytical point of view, the quantitative assays for rheumatoid factors show certain advantages over the traditional haemagglutination tests.

Introduction

The measurement of rheumatoid factors in patients with rheumatoid arthritis can provide information about the diagnosis, prognosis and response to therapy of the disease.

The rheumatoid factors are autoantibodies against the Fc fragment of the immunoglobulin G (IgG).

The antibodies measured in most laboratory assays are of the IgM class, although they also appear in other immunoglobulin classes (1).

The classical method for the determination of the rheumatoid factors is the *Rose-Waaler* haemagglutination assay (2, 3).

This semi-quantitative dilution assay is difficult to standardize, has a poor reproducibility and is rather laborious.

To overcome some of these problems, we have used for several years a modified *Rose-Waaler* assay in our laboratories (4).

Recently several new automated analysers and techniques for the quantitative determination of rheumatoid factors have become available.

They consist of radio-(5) and enzyme-immunoassays (6), or nephelometric (7) and turbidimetric methods (8, 9).

In this study we describe an evaluation of five quantitative rheumatoid factor assays, one semi-quantitative latex test and two modified *Rose-Waaler* assays. These tests all measure the IgM anti-IgG antibodies.

The results are compared with those determined with the traditional *Rose-Waaler* method.

Materials and Methods

(Semi-)quantitative rheumatoid factor tests

The classical *Rose-Waaler* assay was carried out by the Central Laboratory of the Blood Transfusion Service of the Dutch Red Cross, at Amsterdam. All other tests were carried out by us according to the protocols of the manufacturers.

The tests are:

Quantitative assays (A – E):
A: Beckman Array (Beckman Instruments, Inc, Brea, CA, USA).
B: Beckman ICS (Beckman Instruments, Inc, Brea, CA, USA).
C: Behring BNA (Behringwerke AG, Marburg, Federal Republic of Germany).
D: Diesse TasoMatic (Diesse, Monteriggioni (Si), Italy).
E: Hoffmann-LaRoche Cobas-Bio (Hoffmann-LaRoche, Basle, Switzerland)/Orion (Orion Diagnostica, Espoo, Finland).
Semi-quantitative assays (F – I):
F: Cellognost-RF-micro (Behringwerke AG, Marburg, Federal Republic of Germany).
G: RAHA (Fujirebio Inc, Tokyo, Japan).
H: RF-tube test (Hoffman-LaRoche, Basle, Switzerland).
I: *Rose-Waaler.*

The main characteristics of the nine rheumatoid factor tests and the instruments involved are shown in table 1. We have classified the Diesse TasoMatic (D) under the quantitative methods although this instrument gives its results in a stepwise manner: < 50, 50, 60, 70 to 200 by steps of 10 IU/ml, 225, 250, 300 and > 350 IU/ml.

Patient samples

The samples were obtained from patients visiting the rheumatology and pulmonary departments of our hospitals (tab. 2).

The diagnosis, rheumatoid arthritis, was obtained by the rheumatologists using the American Rheumatism Association criteria (10).

The blood samples were collected by venepuncture in vacutainer SST tubes (Becton and Dickinson, Rutherford, NJ, USA) and allowed to clot. The serum was removed and, in order to avoid repeated freezing and thawing, divided into aliquots and stored at −20 °C until assay.

All samples were inactivated by incubating for 30 minutes at 56 °C, except for the method of Diesse Taso-Matic (D) and the RF-tube test (H).

For both Beckman methods, Array (A) and ICS (B), the inactivated samples were centrifuged at 8000 *g* for five minutes.

Standardisation and controls

For the titration methods the "Relares serum" (the Dutch reference serum preparation for rheumatoid factors related to the "international reference preparation of rheumatoid arthritis serum of the WHO") (11) was used as a standard to convert titres to IU/ml.

For the preparation of this "Relares serum", plasma was first obtained by plasmapheresis from 20 patients with rheumatoid arthritis. Serum was then prepared by recalcification and di-

Tab. 1. Main characteristics of the nine (semi-)quantitative tests used for the rheumatoid factor assays. CDC = Center of Disease Control.

Method	Instruments, principles and reagents	Standard related to	Reference values (IU/ml)	Measuring range (IU/ml)
A	Beckman Array Rate nephelometry Rheumatoid factor reagent	CDC	< 60	60–2350
B	Beckman ICS Rate nephelometry Rheumatoid factor reagent	CDC	< 60	60–400
C	Behring BNA Endpoint nephelometry NA latex-RF reagent	WHO	< 17	17–3540
D	Diesse TasoMatic Latex turbidimetry Ra-tec reagent	WHO	< 50	50–350
E	Hoffmann-LaRoche Cobas-Bio Immuno-turbidimetry Orion reagents for Rheumatoid Factors	WHO	< 15	15–100
F	Cellognost-RF-micro Haemagglutination dilution (modified *Rose-Waaler*)	Relares	< 50	–
G	RAHA Haemagglutination dilution (modified *Rose-Waaler*)	Relares	< 10	–
H	RF-tube test Direct latex-agglutination dilution	Relares	< 25	–
I	*Rose-Waaler* Haemagglutination dilution	Relares	< 12.5	–

Tab. 2. The origin of the 196 patient samples.

Clinical diagnosis	Number
1. Classical rheumatoid arthritis	95
2. Definitive rheumatoid arthritis	25
3. Ankylosing spondylitis	58
4. Morbus *Reiter*	5
5. Reactive arthritis	2
6. Systemic lupus erythematosus	4
7. Sarcoidosis	7
Total number	196

vided into ampoules and lyophilized. After reconstitution with 1 ml distilled water the values were determined by Relares (Reference Laboratory Reuma-serology) by comparison with the WHO reference serum of 100 IU/ml. The "Relares serum" gave a value of 400 IU/ml in the *Rose-Waaler* test and 200 IU/ml in the Latex-tests.

For the five quantitative methods the standard(s) provided with the kits were used. The standard used for the Behring BNA (C), Diesse TasoMatic (D) and Cobas-Bio/Orion (E) is related to the WHO reference serum. For Beckman Array (A) and Beckman ICS (B) the standard is related to the "American Center of Disease Control National Reference Preparation for rheumatoid factors" (12).

In all semi-quantitative and quantitative assays we used the "Behring Rheumatoid Reference Serum" as a control.

This reference serum consists of a pool of human sera with a high concentration of rheumatoid factors. The reference serum is calibrated according to the *Rose-Waaler* test as recommended by the WHO (11) by comparison with the WHO International Reference Preparation.

In the quantitative tests we used also the "Relares serum" as a control serum.

Statistical analysis

Orthogonal regression analysis was performed according to the method of *Deming* as discussed by *Cornbleet* et al. (13).

The outlayers test described herein was only used in the correlation analyses of the five quantitative tests (A – E). Outlayers were defined as values outside four times the standard error of estimate (13).

Precision between and within runs

Precision studies were performed with the following five quantitative methods: Beckman Array (A), Beckman ICS (B), Behring BNA (C), Diesse TasoMatic (D) and Cobas-Bio/Orion (E).

The within run precision analyses were carried out in pooled patient sera. Each serum was estimated 8 to 12 times. The sera were choosen so that the concentrations of rheumatoid factors were spread over the whole measuring range of the instruments. The value of 499 IU/ml by the Diesse TasoMatic method (D) however was obtained with diluted (9 g/l NaCl) serum.

For the between run precision analyses we used two to four samples in every run. These samples were Behring Rheumatoid Reference Serum for rheumatoid factors, Relares serum, Pooled Patient Serum, Standard 100 IU/ml of Diesse and Calibration Serum of Beckman.

Correlation studies

The titres of the dilution methods were converted to IU/ml before the regression analyses were performed.

For the correlation studies we used the results of all 196 patients, unless one or both values were zero, below the lowest standard or below the detection limit of the method.

Sensitivity, specificity and predictive value (14)

Sensitivity indicates the probability of positive test restults when the disease is present (positivity in disease).

It may be expressed by the following relationship:

$$\text{Sensitivity} = \frac{\text{number of RA-patients with positive test}}{\text{total number of RA-patients}}$$

Specificity indicates the probability of negative test results when the disease is not present (negativity in health).

It may be expressed by the following relationship:

$$\text{Specificity} = \frac{\text{number of patients without RA with negative test}}{\text{total number of patients without RA}}$$

The predictive value of a positive test is expressed by:

$$\frac{\text{number of RA-patients with positive test}}{\text{total number of positive tests}}$$

The predictive value of negative test is expressed by:

$$\frac{\text{number of patients without RA with negative test}}{\text{total number of negative tests}}$$

The predictive value of a positive (negative) test indicates the probability that the disease (RA, rheumatoid arthritis) is present (absent) when the test is positive (negative).

Results and Discussion

Precision within and between runs

The within and between run precision data are given in table 3.

The within run precision was good (< 4%) for the Beckman Array (A) method, the Behring BNA (B) method (except for the value 575 IU/ml) and the Cobas-Bio/Orion (E) method [except near its detection limit of 15 IU/ml (CV = 16% for the value of 19 IU/ml)].

The coefficient of variation of 8.4% for the Behring BNA (B) method was obtained in a pooled patient serum with a mean value of 575 IU/ml. This value is near the beginning of the range requiring dilution of the sample.

The ten results for this pooled serum are shown in table 4. The mean value for the four undiluted samples was 517 IU/ml and for the six automatically diluted samples 614 IU/ml. This difference in mean values might be explained by the use of different parts of the calibration curve.

For the Diesse TasoMatic (D) the within run precision appeared to be satisfactory with a CV < 11%, taking into account the stepwise presentation of the results.

Tab. 3. Precision between and within run (CV%) of the Beckman Array (A), Beckman ICS (B), Behring BNA (C), Cobas-Bio/Orion (D) and the Diesse TasoMatic (E).
All values are in IU/ml.
1 = Behring Rheumatoid Reference Serum. 2 = Relares Serum. 3 = For the Beckman Array (A) the Calibrator, for the Behring BNA (C) pooled serum and for the Diesse TasoMatic (E) the standard 100 IU/l.
The columns 4 to 8 are pooled patient sera, covering the measuring range of the instruments.

Method		Between-run CV			Within-run CV				
		1	2	3	4	5	6	7	8
Beckman Array (A)	n	9	10	9	10	10	10	10	10
	Mean	146	501	215	76	81	145	256	337
	CV%	1.6	4.0	0.7	3.1	3.1	0.7	0.8	0.9
Beckman ICS (B)	n	19	17	–	–	–	–	–	–
	Mean	144	544	–	–	–	–	–	–
	CV%	12.3	7.1	–	–	–	–	–	–
Behring BNA (C)	n	8	10	19	10	10	10	–	–
	Mean	118	280	47	97	575	1938	–	–
	CV%	8.8	5.8	5.5	3.6	8.4	4.0	–	–
Cobas-Bio/ Orion (D)	n	16	16	–	11	12	12	10	10
	Mean	76	208	–	19	25	38	73	103
	CV%	11.6	2.8	–	16.0	2.7	0.8	0.8	0.9
Diesse Taso-Matic (E)	n	39	36	43	9	9	9	9	8
	Mean	90	226	105	76	126	160	198	499
	CV%	11.1	16.7	14.8	7.0	11.2	6.1	10.9	6.9

Tab. 4. Results of the within-run precision study of a pooled patient serum with a value around the automatic dilution step of the Behring BNA method (C). See text for further explanation.

Sample	Results in IU/ml	
	Undiluted	Diluted
1	>528	619
2	523	–
3	503	–
4	518	–
5	>528	631
6	>528	609
7	>528	602
8	>528	601
9	>528	621
10	524	–
Mean	517	614

The between run precision for the Beckman Array (A) and the Behring BNA (C) was good (< 9%), for the other quantitative methods acceptable (< 17%).

The manual titre methods gave a maximal difference of only one dilution step.

Correlation studies

The correlations between the quantitative and semi-quantitative methods and between the semi-quantitative methods themselves are shown in table 5.

It can be seen that the coefficients of correlation (r) between the quantitative methods A – E and the semi-quantitative tests F and I are all below or equal to 0.53. Between the quantitative methods A – E and the RAHA (G) and RF-tube test (H) a higher correlation was observed, i.e. r = 0.65 to r = 0.85.

The coefficients of correlation between each of the semi-quantitative methods (F, G, H and I) were all less than 0.65.

In table 6 the coefficients of correlation between each of the five quantitative tests (A, B, C, D and E) are shown, ranging from r = 0.86 to r = 0.99.

In figures 1 and 2 the serum values obtained with the five quantitative methods A – E are plotted against each other.

The correlation between the quantitative tests themselves is much stronger then between the semi-quantitative and quantitative tests or between the semi-quantitative tests themselves.

This less satisfactory coefficient of correlation can be partly explained by the use of titres. In the conversion of titres to numerical values (IU/ml) a difference of only one dilution step causes the doubling or halving of the value in IU/ml (15).

Tab. 5. *Deming* debiased regression analyses between the quantitative (A–E) and the semi-quantitative methods (F–I) and the semi-quantitative tests (F–I) themselves.
No correction for outlayers was applied here.
n = number of patients; r = coefficient of correlation; b = intercept; a = slope; y = b + ax.
(Vertical method = x; horizontal method = y).

Method		Cellognost-RF-micro (F)	RAHA (G)	RF-tube test (H)	*Rose-Waaler* (I)
Beckman Array (A)	n	50	65	72	61
	r	0.22	0.70	0.72	0.28
	b	−131	89	27	40
	a	0.71	0.50	0.28	0.82
Beckman ICS (B)	n	56	78	87	68
	r	0.33	0.82	0.65	0.46
	b	−150	47	−13	19
	a	0.72	0.55	0.37	0.82
Behring BNA (C)	n	55	75	88	68
	r	0.50	0.78	0.81	0.53
	b	−230	19	−32	−46
	a	1.42	1.06	0.72	1.60
Diesse TasoMatic (D)	n	47	56	59	55
	r	0.47	0.76	0.85	0.47
	b	−429	−94	−119	−204
	a	2.99	2.14	1.49	3.10
Cobas-Bio/ Orion (E)	n	54	72	85	64
	r	0.41	0.75	0.84	0.46
	b	−294	−21	−58	−110
	a	2.05	1.51	1.01	2.28
Cellognost RF-micro (F)	n	–	53	55	55
	r	–	0.57	0.45	0.45
	b	–	192	60	239
	a	–	0.74	0.52	1.09
RAHA (G)	n	–	–	71	61
	r	–	–	0.64	0.53
	b	–	–	−55	−75
	a	–	–	0.69	1.49
RF-tube test (H)	n	–	–	–	66
	r	–	–	–	0.46
	b	–	–	–	53
	a	–	–	–	2.18

Tab. 6. *Deming* debiased regression analyses between the five quantitative methods (A–E) without outlayers.
n = number of patients; r = coefficient of correlation; b = intercept; a = slope; y = b + ax.
(Vertical method = x, horizontal method = y).
e = number of outlayers.

Method		Beckman ICS (B)	Behring BNA (C)	Diesse Taso-Matic (D)	Cobas-Bio/ Orion (E)
Beckman Array (A)	n	59	68	56	65
	r	0.99	0.95	0.86	0.98
	b	38	46	86	40
	a	0.96	0.50	0.20	0.34
	e	17	6	1	9
Beckman ICS (B)	n	–	84	56	77
	r	–	0.98	0.89	0.98
	b	–	26	52	−7
	a	–	0.75	0.30	0.56
	e	–	15	4	12
Behring BNA (C)	n	–	–	54	80
	r	–	–	0.97	0.98
	b	–	–	9	7
	a	–	–	0.58	0.74
	e	–	–	6	8
Diesse TasoMatic (D)	n	–	–	–	53
	r	–	–	–	0.98
	b	–	–	–	2
	a	–	–	–	1.20
	e	–	–	–	5

Standardisation and controls

Semi-quantitative methods

In order to convert titres to IU/ml for each method in every run the Relares serum was assayed. After all assays were complete, the mean titre of the Relares serum was compared with its target value in IU/ml (16).

For the Cellognost-RF-micro (F), a titre of 1:80 corresponded to 400 IU/ml, for the RAHA (G) a titre of 1:2560 represented 300 IU/ml, while for the RF-tube-test (H) a titre of 1:160 represented a value of 200 IU/ml. For the *Rose-Waaler* method (I) the Relares serum was used as a standard (400 IU/ml) in every run to convert the titres into IU/ml.

In every run also the Behring Rheumatoid Reference serum was assayed. For the Cellognost-RF-Micro (F) a value of 200 IU/ml was found, for the RAHA (G) 50 IU/ml and for the RF-tube test (H) 75 IU/ml.

For the *Rose-Waaler* method this Behring Rheumatoid Reference Serum was assayed twice at 100 IU/ml.

Quantitative methods

Data were first obtained by using the standards supplied with the kits. In addition the Relares Serum and the Behring Rheumatoid Reference Serum were analysed in every run. Table 7 shows the mean values and standard deviations for these two sera.

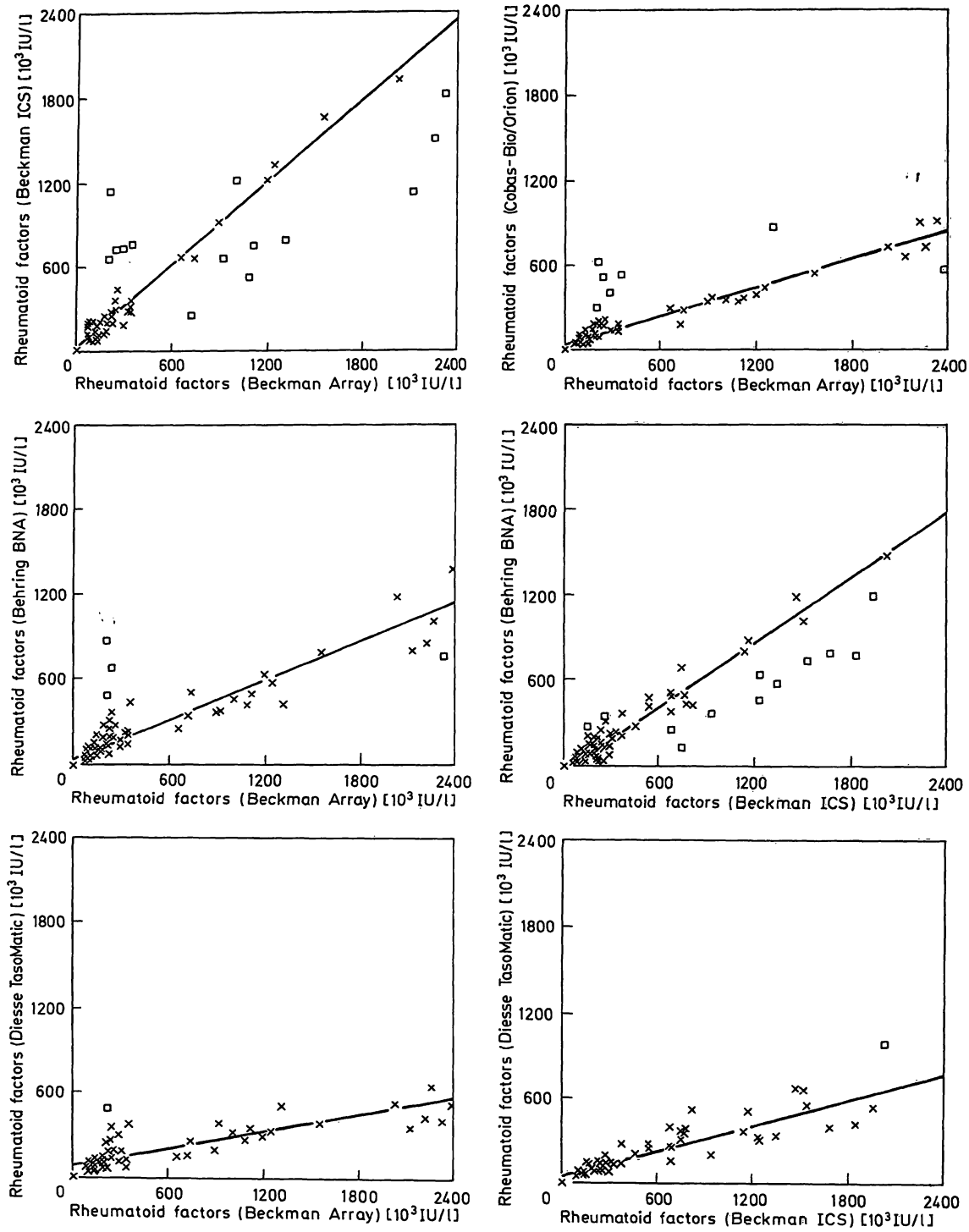

Fig. 1. Graphs showing the correlations between the quantitative rheumatoid factor assays. All values are in IU/ml. □ = outlayer in *Deming* debiased orthogonal regression analyses.

It should be mentioned that the standards used in methods A and B were related to the reference preparation of the Center of Disease Control, but for the other methods (C, D and E) to that of the WHO.

The value of the Center of Disease Control Reference Preparation is 2.3 times the value of the WHO (17).

Therefore in table 7, the values of "Relares" and "Behring" sera for methods A and B are also given in WHO units.

The values for the Relares serum obtained with the quantitative methods, all related to the WHO units, are now between 208 and 280 IU/ml and the values for the Behring Rheumatoid Reference Serum between 62 and 118 IU/ml.

In spite of standardisation using the well defined WHO Reference Preparation for the quantitative tests C, D and E and using the Center of Disease Control Reference Preparation for the methods A and B, there

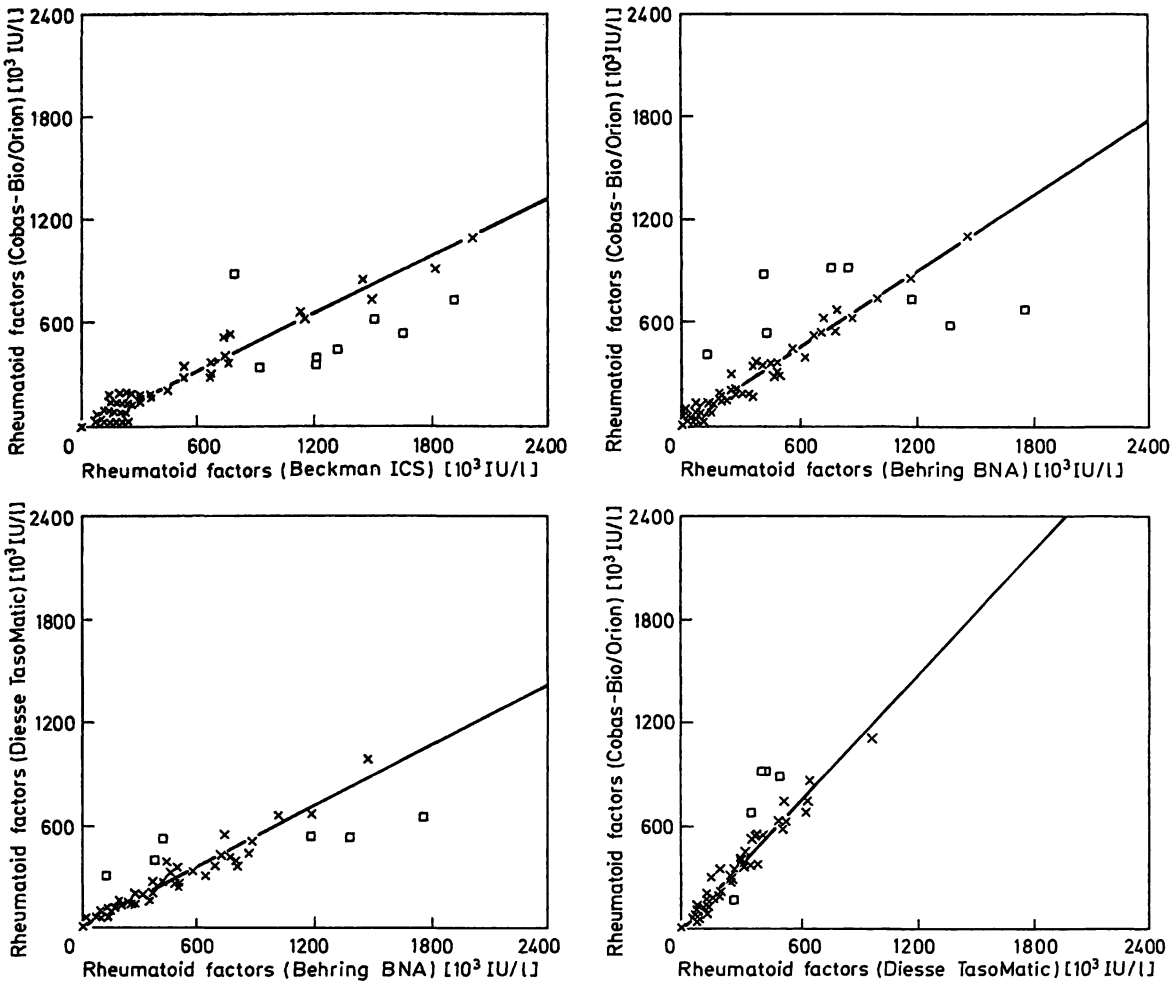

Fig. 2. Graphs showing the correlations between the quantitative rheumatoid factor assays. All values are in IU/ml. □ = outlayer in *Deming* debiased orthogonal regression analyses.

Tab. 7. Values of the Relares serum and Behring Rheumatoid Reference Serum related to the WHO units for methods C, D and E and to the Center of Disease Control units for methods A and B.
The values in the second column in brackets by methods A and B are obtained after conversion of the Center of Disease Control units to WHO units. (Here we used: Center of Disease Control = 2.3 × WHO).

Method	Standard related to:	"Relares" mean and [S.D.] IU/ml	"Behring" mean and [S.D.] IU/ml
Beckman Array (A)	CDC (WHO)	501 [20] (218)	146 [2] (63)
Beckman ICS (B)	CDC (WHO)	544 [39] (237)	144 [12] (62)
Behring BNA (C)	WHO	280 [16]	118 [10]
Diesse TasoMatic (D)	WHO	226 [38]	90 [10]
Cobas-Bio/ Orion (E)	WHO	208 [6]	76 [8]

was a large systematic difference in the actual values found. These differences were observed for the patient sera (tab. 6, figs. 1 and 2) as well as for the Relares Serum and the Behring Rheumatoid Reference Serum (tab. 7).

This discrepancy in bias might be explained by the variability of the IgG antibodies used in the various kits. Another explanation could be the difference in the origin of the rheumatoid factor preparations used as standards in the kits, since these rheumatoid factors are a group of diverse globulins.

We also investigated the number of positive patient sera which exceeded the measuring ranges of the kits. A large difference was found between the methods used; see table 8.

Sera showing values above the upper limit of the measuring range were diluted 1 : 6. Further dilution was necessary for sixteen of the sera, but only for the Cobas-Bio/Orion method.

Tab. 8. Proportions of patient sera reanalysed because values exceeded the measuring ranges of the various methods.

Method	Total positives of the 196 patient sera	Exceeding measured range	
		n	%
Beckman Array (A)	80	3	4%
Beckman ICS (B)	85	27	32%
Behring BNA (C)	109	0	0%
Diesse TasoMatic (D)	67	17	25%
Cobas-Bio/Orion (E)	91	48	53%

In table 9 the sensitivity, specificity, the positive and the negative predictive values of the methods used (A – I) are shown.

With regard to these calculations we divided the patients into two groups. The first group consisted of the patients suffering from classical rheumatoid arthritis and definitive rheumatoid arthritis, i.e. numbers one and two from table 2. The second group consisted of the patients suffering from other diseases, such as reactive arthritis, sarcoidosis, ankylosing spondylitis, Morbus *Reiter* and systemic lupus erythematosus, i.e. numbers three to seven from table 2.

Table 9 shows that of the semi-quantitative methods (F – I), the RF-tube test (H) gives the best results. The quantitative methods (A – E) do not show identical results.

The clinical usefulness of the quantitative tests seems identical to, or better than the traditional *Rose-Waaler* method (I) or the other semi-quantitative tests (F, G and H); see table 9. However, from the analytical point of view we recommend the use of one of the quantitative tests for the determination of the rheumatoid factors, with patient results expressed in IU/ml.

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Tab. 9. Sensitivity, specificity and predictive values of positive and negative results of the various methods in "RA" and "no-RA" patients. See text for further explanation.
RA = rheumatoid arthritis.

Method	Patient classification			Sensitivity	Specificity	Predictive value of	
		Pos.	Neg.	%	%	pos. test %	neg. test %
Beckman Array (A)	RA	74	34				
	no-RA	4	70	69	95	95	67
Beckman ICS (B)	RA	72	39				
	no-RA	10	64	65	86	88	62
Behring BNA (C)	RA	96	15				
	no-RA	11	61	86	85	90	80
Diesse TasoMatic (D)	RA	64	49				
	no-RA	2	72	57	97	97	60
Cobas-Bio/ Orion (E)	RA	85	27				
	no-RA	6	67	76	92	93	71
Cellognost RF-micro (F)	RA	59	52				
	no-RA	2	72	53	97	97	58
RAHA (G)	RA	71	38				
	no-RA	6	68	65	92	92	54
RF-tube test (H)	RA	87	24				
	no-RA	3	71	78	96	97	75
Rose-Waaler (I)	RA	68	43				
	no-RA	2	72	61	97	97	63

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